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EXAMINER

SIMS, JASON M

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DETAILED ACTION

Applicant's arguments, filed 7/14/2008, have been fully considered. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Applicants have amended their claims, filed 7/14/2008, and therefore rejections newly made in the instant office action have been necessitated by amendment.

Applicant has newly added claims 21-28 in the response filed 7/14/2008, which have been acknowledged and entered.

Claims 14 and 20-28 are the current claims hereby under examination.

The following rejection has been modified, which is necessitated by amendment:

Claim Rejections - 35 USC § 112-modified

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14, 21-26, and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an intracellularly binding immunoglobulin molecule comprising the amino acid sequence of SEQ ID NO: 3 and a variable light chain wherein said immunoglobulin specifically binds BCR or BCR-ABL, does not reasonably provide enablement for i) an intracellularly binding immunoglobulin molecule comprising a variable heavy chain which exhibits 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 3 and a variable light chain, which does not specify to what

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it binds, or ii) an intracellularly binding immunoglobulin molecule comprising a variable heavy chain which exhibits 95%, 96%, 97%, 98%, or 99% identity to SEQ ID NO: 3 and a variable light chain which binds to BCR or BCR-ABL. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). These factors include, but are not limited to:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

The claim is broad because the claim encompasses an intracellularly binding immunoglobulin molecule comprising a variable heavy chain which exhibits at least 95% homology to the consensus sequence SEQ ID No 3; and a variable light chain. Therefore, the claim encompasses a 5% variability within the variably heavy chain to the consensus sequence SEQ ID No 3, which comprises 112 amino acid residues and 5% equals approximately 5.6 amino acid residues. Essentially, there may be a 5.6 residue

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difference from SEQ ID No. 3, such as the first 5-6 amino acids, with each residue having 4 options, which results in approximately 983 unique combinations at one time. The number of unique combinations increases dramatically again when taking into consideration the number of combinations involving the 5-6 residues that may vary throughout the entire SEQ ID No. 3. With regards to enablement, one of ordinary skill in the art would not know which amino acids within the CDR regions may vary up to 5%, 4%, 3%, 2%, or even 1% of the seq ID No 3. Without knowing which amino acids may vary within the CDR region, one of ordinary skill in the art would have an undue amount of experimentation with determining which amino acids, if varied, would prohibit binding or activity. Moreover, this is specifically true with regards to the effect on the binding functionality when the binding is not specific. Therefore, one of ordinary skill in the art would be left with undue experimentation when determining to what the immunoglobulin binds and which amino acids can vary without effecting the binding functionality with respect to the vast antigen binding options.

The nature of the invention

The nature of the invention is found with immunology and the level of skill is high.

The state of the prior art and the level of predictability

A number of scientific challenges are present in understanding a correlation between varying amino acid residues in a variable heavy chain while maintaining binding function or will maintain its intracellular binding. Specifically, there is a large

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amount of experimentation necessary when determining which amino acids within a CDR region may vary without effecting binding functionality. Generally, there are number of art-related disclosures that illustrate that the art as it pertains to the claimed invention is unpredictable. It is understood from the instant specification that SEQ ID No. 3 is a conserved sequence in the variable heavy chain. A conserved sequence within a binding domain typically involves key residues for maintaining function, such as those found within the CDRs. Therefore, a substitution of one amino acid or even 5-6 amino acid substitutions of key residues can have unpredictable results. For example, Chiba et al. (P/N 5,171,838) at col. 5, lines 3-5 describes that “a particular amino acid substitution on Leu3a binding activity is often somewhat unpredictable.” Chiba et al. does teach that certain “key” residues may be readily substituted without sacrifice of biological activity, but these are known residues in the instant reference. Boehncke et al. (1992) in the abstract teaches that particular amino acid substitutions such as those substitutions with larger side chains often diminished activity. Furthermore, Boehncke et al. (1992) teaches at the abstract that the change in the peptide altered the extent of binding. In addition, Lowman et al. (US A/N 2003/0228663) at paragraph [0256] states that “these types of substitutions in general had unpredictable effects on binding affinity.” Therefore, without guidance, the art describes a large amount of unpredictability with determining which amino acids within key regions, i.e. CDRs, may vary without effecting functionality. Without knowing which amino acids may vary within the CDR region, one of ordinary skill in the art would have an undue amount of experimentation with determining which amino acids, if varied, would prohibit binding or

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activity. Moreover, this is specifically true with regards to the effect on the binding functionality when the binding is not specific. Therefore, one of ordinary skill in the art would be left with undue experimentation when determining to what the immunoglobulin binds and which amino acids can vary without effecting the binding functionality with respect to the vast antigen binding options.

The amount of guidance and existence of working examples

In the detailed description of the specification and in Fig. 5 applicants describe an intracellularly binding immunoglobulin comprising a variable heavy chain, which exhibits a variety of homology to the consensus sequence SEQ ID No 3. However, there were no examples found that described which amino acid residues could be substituted without effecting or prohibiting the binding function of the immunoglobulin. Therefore, there is not found guidance as to which 5%, 4%, 3%, 2%, or even 1% of the amino acid substitutions of consensus sequence SEQ ID No 3, specifically those within the CDRs, would prohibit the immunoglobulin to maintain binding functionality. Moreover, this is specifically true with regards to the effect on the binding functionality when the binding is not specific. Therefore, one of ordinary skill in the art would be left with undue experimentation when determining to what the immunoglobulin binds and which amino acids can vary without effecting the binding functionality with respect to the vast antigen binding options.

The Quantity of Experimentation

Based on the art cited above, the unresolved issues in the relevant art pertaining to the unpredictability of protein function based on amino acid substitutions, the amount of non-routine experimentation required would be high. It is well known in the art that single or multiple substitutions or deletions can alter biomolecular function in many instances, albeit not all. In the absence of any factual evidence that characterizes the structural and functional components of a biomolecule, the effects of these changes are largely unpredictable as stated above. In the instant specification it is unclear as to which residues are "key" residues in Seq ID No 3 and therefore it is unpredictable as to which amino acid substitutions will enable the immunoglobulin to maintain its binding function. Without such information as to the "key" binding residues of the variable heavy chain, the amount of experimentation necessary to determine which amino acid substitutions would not result in a lack of binding functionality would be undue.

Accordingly, in order to enable the invention as claimed, one of ordinary skill in the art would have to resort to undue experimentation.

Response to Arguments:

Applicant's arguments filed 7/14/2008 have been fully considered but they are not persuasive.

Applicant argues that the specification provides ample guidance for producing intracellular immunoglobulin molecules with a 95% homology to SEQ ID NO: 3 and thus fully enables the production and use of intracellularly immunoglobulins.

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Applicant's argument is not found persuasive because ample guidance as to which amino acids may vary within the CDRs and yet enable the immunoglobulin to maintain binding functionality. Furthermore, ample guidance as to how these amino acid variations may change with regards to retaining binding functionality with one antigen to another. In addition, there is not ample guidance as to what else an intracellularly binding immunoglobulin with 95% homology in the variable heavy region may have binding functionality. Therefore, to determine all the different potentially bindings, how the amino acid sequences may vary in the CDRS to retain the binding functionality, would cause an undue amount of experimentation to one of ordinary skill in the art.

Applicant further argues that the specification provides examples of mutations in the framework and CDR regions wherein the immunoglobulin maintains binding to BCR.

Applicant's arguments are not found persuasive as they are not commensurate in scope with the claimed invention, which is drawn to general binding functionality. Therefore, one of ordinary skill in the art would not know which sequences could vary wherein the immunoglobulin may maintain general binding functionality and to what else it may bind.

Applicant further argues that the reference Chiba et al. does not support an unpredictability and therefore does not support a case for a lack of enablement.

Applicant's arguments are not found persuasive as Chiba et al. reference discloses that those "key" residues are known and the functionality is specifically described. Chiba et al. also states that knowing which amino acids can be substituted

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can be unpredictable. Therefore, without guidance as to what the specific binding functionality of an immunoglobulin and what amino acids may be substituted and the immunoglobulin retain binding functionality, an undue amount of experimentation would be necessary.

Applicant further argues that board decisions support applicants position for enablement.

Applicant arguments are not found persuasive because applicants provide only one example to which the immunoglobulin may bind, i.e. BCR or BCR-ABL, but the claims encompass any binding activity. Therefore, to what else the immunoglobulin may bind, itself presents an undue amount of experimentation. Furthermore, to determine what amino acid residues may vary while the molecule retains binding activity further presents an undue amount of experimentation. Therefore, the scope of the claims must bear a reasonable correlation with the scope of enablement. See *In re Fisher*, 166 USPQ 19 24 (CCPA 1970).

Allowable Subject Matter

Claims 20 and 27 are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jason Sims, whose telephone number is (571)-272-7540.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Marjorie Moran can be reached via telephone (571)-272-0720.

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Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the Central PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The Central PTO Fax Center number is (571)-273-8300.

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// Jason Sims //

/Michael Borin/
Primary Examiner, Art Unit 1631